

**TRAINING FOR THE HEALTH SECTOR**  
*[Date ...Place ...Event...Sponsor...Organizer]*

---

**DEVELOPMENTAL & ENVIRONMENTAL  
ORIGINS OF ADULT DISEASE**

**Children's Health and the Environment**

WHO Training Package for the Health Sector

World Health Organization

*www.who.int/ceh*

*October 2011*

10/19/2011

1

<<NOTE TO USER: Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation in the space indicated.>>

<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the problem. Present only those slides that apply most directly to the local situation in the region.>>

<<NOTE TO USER: Both embryonic and fetal origins of adult disease will be considered in this presentation. The end of the eighth week of gestation marks the end of the "embryonic period" and the beginning of the "fetal period">>

<<NOTE TO USER: This module presents several examples of risk factors that affect development, you can find more detailed information in other modules of the training package that deal with specific risk factors, such as lead, mercury, pesticides, persistent organic pollutants, endocrine disruptors; or disease outcomes, such as neurodevelopment effects, immune effects, respiratory effects, and others.>>

## Developmental & environmental origins of adult disease

### LEARNING OBJECTIVES

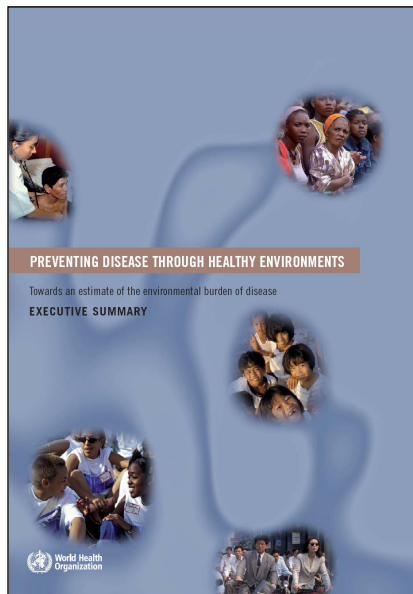
#### AFTER THIS PRESENTATION, INDIVIDUALS WILL BE ABLE TO:

- ❖ Explain why risks to the unborn child and the infant from environmental hazards are unique
- ❖ Illustrate the increased and unique vulnerabilities of the fetus and the neonate to environmental challenges and threats and how these can predispose to disease later on in life
- ❖ Propose remedial and preventive actions

After this presentation, individuals will be able to:

- ❖ Explain why risks to the unborn child and the infant from environmental hazards are unique
- ❖ Illustrate the increased and unique vulnerabilities of the fetus and the neonate to environmental challenges and threats and how these can predispose to disease later on in life
- ❖ Propose remedial and preventive actions

## Developmental & environmental origins of adult disease



WHO

10/19/2011

### Attributable to environmental factors:

- **24% of global disease burden** (healthy life years lost)
- **23% of all deaths** (premature mortality)
  - **25% in developing countries**
  - **17% in developed regions**
  - **36% in children 0-14 years**

3

WHO has published an important report on *Preventing Disease Through Healthy Environments*. This report confirms that approximately one-quarter of the global disease burden, and more than one-third of the burden among children, is due to modifiable environmental factors. The analysis here also goes a step further, and systematically analyzes how different diseases are impacted by environmental risks... and by 'how much.' Heading that list are diarrhoea, lower respiratory infections, various forms of unintentional injuries, and malaria. This 'environmentally-mediated' disease burden is much higher in the developing world than in developed countries - although in the case of certain non-communicable diseases, such as cardiovascular diseases and cancers, the per capita disease burden is larger in developed countries. Some 2.5 million people die every year from cardiovascular disease attributable to environmental factors, including work-related stress, as well as chemical, air pollution, and second hand smoke exposures.

Children bear the highest death toll with more than 4 million environmentally-caused deaths yearly, mostly in developing countries. The infant death rate from environmental causes is 12 times higher in developing than in developed countries, reflecting the human health gain that could be achieved by supporting healthy environments.

Ref:

•WHO. Preventing disease through healthy environments: Towards an estimate of the environmental burden of disease. Pruess-Ustun A., Corvalan C. WHO, Geneva, Switzerland. 2006

## **Developmental & environmental origins of adult disease**

### **The children of today – increased rates of**

- ❖ Asthma & lung disease
- ❖ Obesity, diabetes, cardiovascular disease
- ❖ Learning disabilities, IQ issues
- ❖ Reproductive organ disorders
- ❖ Some forms of cancer
- ❖ Other

### **EARLY ENVIRONMENTAL ORIGINS OF DISEASE?**

10/19/2011

4

<<READ SLIDE.>>

*Ref:*

- Neira M et al. Environmental threats to children's health – a global problem. *Int J Environment and Health*, 2008, 2(3/4):276.
- Pronczuk J, Bruné MN, Gore F. Children's environmental health in developing countries. In: *Encyclopedia of Environmental Health*. J. Nriagu, ed. Elsevier, 2011.
- Trasande L, Landrigan PJ. The National Children's Study: a critical national investment. *Environ Health Perspect*, 2004, 112(14): A789–A790.
- WHO. Children's health and the environment: a global perspective. Pronczuk J, ed. *WHO*, Geneva, 2005

## Developmental & environmental origins of adult disease

### **DEVELOPMENTAL ORIGINS OF HEALTH & DISEASE**

**This concept proposes that components of the developmental environment: mother's nutrition, body composition, stress levels, lifestyle & exposure to chemicals and toxicants, act via developmental plasticity to alter the ways in which the embryo, fetus and infant develop.**

**Result of these processes affects responses of the offspring to environmental challenges and thus the risk of non-communicable disease**

10/19/2011

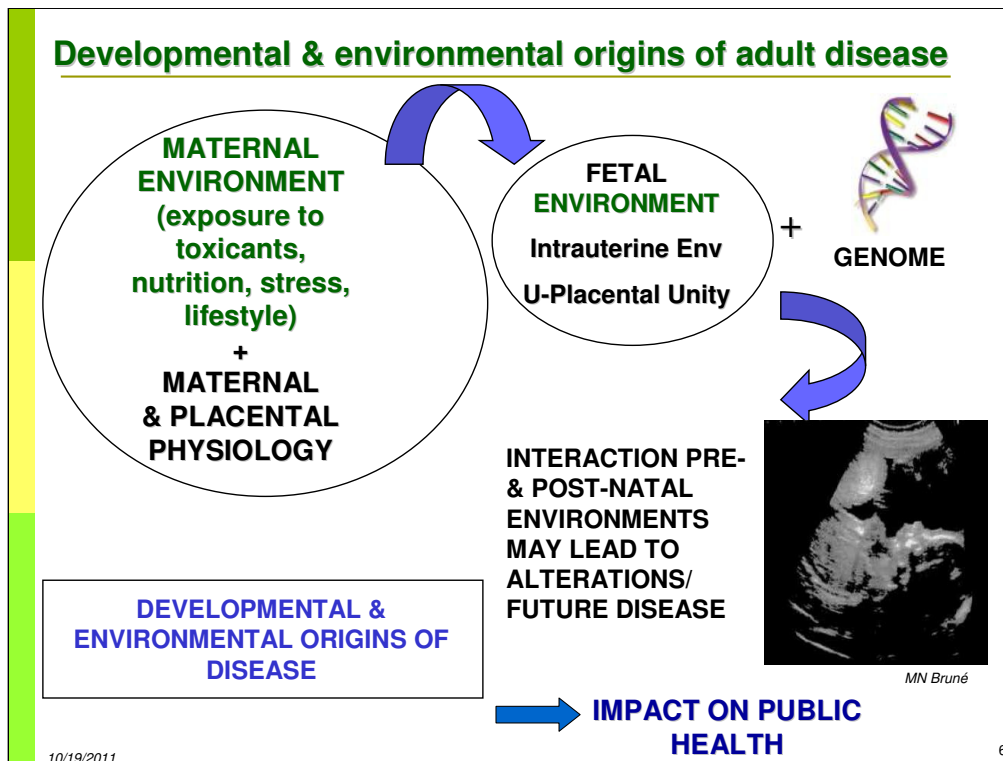
5

The Developmental Origins of Health and Disease (DOHaD) concept proposes that a range of components of the developmental environment, in particular mother's nutrition, body composition, stress levels, lifestyle and exposure to chemicals and toxicants, act via developmental plasticity to alter the ways in which the embryo, fetus and infant develop. These processes act across the normal range of human development, and do not merely operate at the extremes. They do not necessarily produce a reduction in fetal growth, for example. The result of these processes is to affect the responses of the offspring to environmental challenges and thus the risk of non-communicable diseases.

According to current thinking, coronary heart disease and related disorders arise through a series of interactions between environmental influences and the pathways of development that precede them. Thus these diseases are the product of branching development pathways, which are triggered by the environment both before and after birth. Maternal influences (e.g. body composition, dietary balance), are known to have long-term effects on adult disease, without necessarily affecting size at birth. For instance, several studies have demonstrated that underweight women are more likely to have infants that go on to develop a resistance to insulin in adulthood, an association that can only be partly attributed to a low birth weight.

#### *Refs:*

- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59.
- Grandjean. P. Prenatal programming and toxicity. *Basic and Clinical Pharmacology and Toxicology*, 2008, 102:2.
- WHO. Promoting optimal fetal development: report of a technical consultation. *WHO*, Geneva, Switzerland, 2006.



Fetal growth is determined by the interaction between the environment and the fetal genome. The fetal environment is determined by the maternal environment and by maternal and placental physiology. There is evidence that the interaction between the fetal environment and genome can determine the risk of postnatal disease, as well as the individual's capacity to cope with the postnatal environment.

Exposure to environmental pollutants inhaled, or introduced with food by the mother during pregnancy, may disrupt the epigenetic setting of embryo and foetus cells, interfering with cells' differentiation, adversely affecting the planning and development of various organs and tissues, opening the way to metabolic disorders, neuro-endocrine, neuro-degenerative and even neoplastic diseases that may occur years/decades later, in adulthood.

**Refs:**

- Braun JM et al. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environ Health Perspect*, 2006, 114(12):1904–1909
- Gluckman P, Hanson M. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatric Research*, 2004, 56(3): 311
- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59
- Gluckman, P et al. Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*, 2008, 359:61-73
- Gluckman, P. et al. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proceedings of the Royal Society of London - Series B: Biological Sciences*, 2005, 272: 671-677
- Hertz-Picciotto I et al. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. *Basic Clin Pharmacol Toxicol*, 2008, 102(2):146-54.
- Perera FP et al. A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. *Neurotoxicology*, 2005; 26(4):573–587
- Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature*, 2007, 447(7143):425–432
- Santos F, Dean W. Epigenetic reprogramming during early development in mammals. *Reproduction*, 2004, 127(6):643–651
- Zawia NH, Basha MR. Environmental risk factors and the developmental basis for Alzheimer's disease. *Rev Neurosci*, 2005, 16(4):325-37

Picture provided by MN Bruné

## Developmental & environmental origins of adult disease

### GENETIC MODIFICATIONS

#### Epigenetics:

**Changes in gene function that cannot be explained by changes in the DNA sequence**

#### **3 main types of epigenetic information:**

- ❖ DNA methylation
- ❖ Histone modification
- ❖ Small non-coding RNAs

- **Changes can be permanent or transient**
- **Some of them are part of normal development**
- **Some are affected by environment → altered gene expression (suppression/activation of genes)**

10/19/2011

7

Epigenetic changes are changes in gene function and expression, that could be passed on to the next generation, but are not explained by changes in chromosomal system or DNA sequence.

These changes are part of normal development but some could be determined by environmental exposures – and explain programming.

There are 3 main types of epigenetic information

- DNA methylation – contributes to the regulation of gene expression.
- Histone modifications – have a key role in transcriptional regulation.
- Small non-coding RNAs

These epigenetic changes are the basis for imprinting processes that determine the expression of maternal or paternal alleles in early development. However, the extent of such processes extends beyond imprinting.

#### *Refs:*

- Gluckman, P et al. Effect of *in utero* and early-life conditions on adult health and disease. *New England Journal of Medicine*, 2008, 359:61-73
- Pray LA. Epigenetics: Genome, Meet Your Environment. *The Scientist* 2004, 18(13):14

## Developmental & environmental origins of adult disease

### HOW DOES THE FETUS RESPOND TO AN ADVERSE ENVIRONMENT?

**"Thrifty phenotype hypothesis" proposes that it makes irreversible changes in its development**

- ❖ **Pancreas development and insulin secretion/action**
- ❖ **Altered vascularity and cardiovascular responses**
- ❖ **Reduced number of nephrons**
- ❖ **Changes in deposition of fat, muscle and bone**
- ❖ **Changes in growth & development of many organs such as the liver**
- ❖ **Changes in the set points of control systems such as the hypothalamic-pituitary-adrenal axis**
- ❖ **Changes in metabolic function and control, e.g. via mitochondrial function**

10/19/2011

8

The thrifty phenotype hypothesis proposed by Barker and Hales explains that the fetus responds to adverse environment by making irreversible changes in its development. Specially by reducing its growth to keep the energy for cardiac function and neurodevelopment. Possible explanation: once mature, the individual who - as a fetus - was adapted to a nutritionally deprived environment, carries abnormalities of insulin secretion and activity, reduced vascularity in organs and reduced number of nephrons. Then, if the person becomes obese at middle age, cardiovascular and metabolic diseases may appear as his/her organs and systems are unable to "adapt" to nutritional and other stresses. This model has its limitations: it can explain consequences of extreme intrauterine growth retardation but not how mild shifts in normal development or how exposure at a critical moment can lead to long-term consequences. This model evolved then into the models of the following slides.

#### *Refs:*

- Ashworth CJ et al. Nutritional programming of physiological systems throughout development. *Trends in Developmental Biology*, 2005, 1:117-129.
- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59
- Gluckman, P et al. Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*, 2008, 359:61-73
- Gluckman, P. et al. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proceedings of the Royal Society of London - Series B: Biological Sciences*, 2005, 272: 671-677
- Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull*, 2001, 60:5-20

## Developmental & environmental origins of adult disease

### PREDICTIVE ADAPTIVE RESPONSES (PARs)

- ❖ Theory that the developing organism predicts its future environment
- ❖ Embryo/fetus depend on the information transmitted by the mother/placenta to evaluate/predict the present and future environments
- ❖ **Predictive adaptive responses (PARs):** decisions to change the course of development for future advantages

- **Appropriate PARs**
- **Inappropriate PARs**



10/19/2011

EHP

9

There are adaptive responses that may be made by the developing organism in response to the expected future environment.

• Predictive Adaptive Responses (PARs): these decisions made by the developing organism to change the course of development might be made for future advantages. PARs can be appropriate or inappropriate, this depending on whether the physiological responses the mature organism can have are adapted to the environment it is exposed to.

- The appropriate PARs happen when the physiological responses of the child/adult are adapted to the environment he/she is exposed to.

- When this is not the case, in the inappropriate PARs, the risk of disease in later life is greater.

PARs only happen during critical windows of development when developmental plasticity operates. These windows differ for different organs.

• The key idea in the PARs model is that the developing organism has to predict its future environment quite accurately. The embryo and the fetus depend on the mother and placenta to transmit them information and therefore evaluate the current and future environment. These metabolic, nutrient and hormonal signals can suffer from interference by maternal or placental dysfunction.

• Finally, adaptive responses can be immediately adaptive or predictively adaptive. For example, insulin resistance can be advantageous before and after birth in poor nutritional environments but it also creates a disease risk in the future according to the environment the child/adult will be living in.

#### Refs:

• Barker, DJP et al. Fetal origins of adult disease: strengths of effects and biological basis. *International Journal of Epidemiology*, 2002, 31:1235.

- Gluckman P, Hanson M. Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatric Research*, 2004, 56(3): 311

• Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59

• Gluckman, P et al. Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*, 2008, 359:61-73

• Gluckman, P. et al. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proceedings of the Royal Society of London - Series B: Biological Sciences*, 2005, 272: 671-677

Picture: *Extramurally speaking, Fetal basis of childhood and adult disease: Role of the environment (2002) EHP 110 (6)*. Available at [ehp.niehs.nih.gov/docs/2002/110-6/extram-speaking.html](http://ehp.niehs.nih.gov/docs/2002/110-6/extram-speaking.html) – accessed August 2008.

## Developmental & environmental origins of adult disease

- ❖ Key concept: match/mismatch predictive adaptive responses

Relationship between real and predicted postnatal environments may determine disease risk

- ✓ **Match: low risk of disease**
- ✓ **Mismatch: higher risk of disease**

- ❖ Example - Nutritional signals:

low food availability  $\longrightarrow$  insulin resistance

10/19/2011

10

•The model to explain the “developmental origins of child disease” suggests that the relationship between the predicted and actual mature environments determines disease risk. If the environments match, the risk of disease is low. If they don’t the risk of disease is greater.

•Ideally, the physiological choices established during the plastic and predictive phases (that occur before birth and after birth in the case of some organs) have to be the appropriate ones for the environment of the non-plastic mature phase.

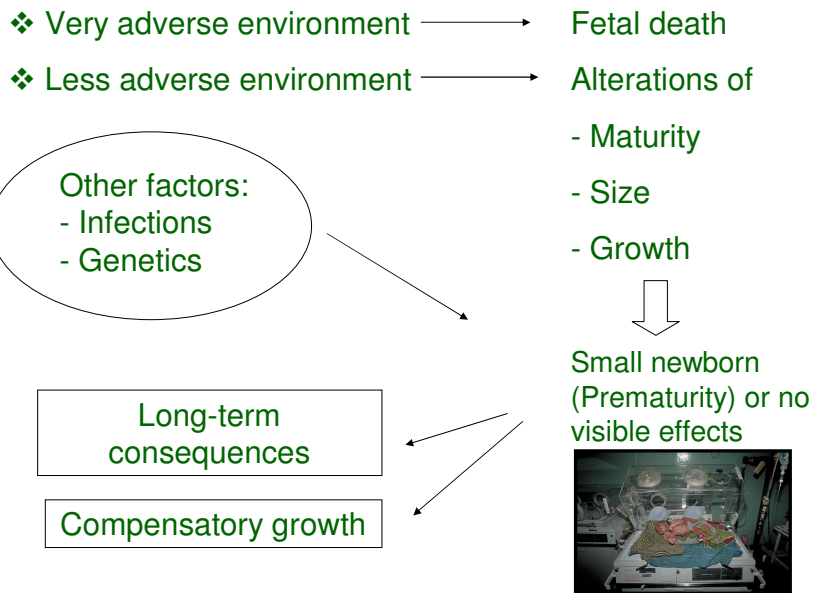
•Example of insulin: during the plastic phases, if nutritional signals show limited food availability, the fetus sets its physiology to have a degree of insulin resistance. The changes become irreversible once the plastic phase is over. But if the environment during the non-plastic phase is too rich, the risk of glucose intolerance increases, possibly leading to diabetes.

As nutritional intakes in childhood and adulthood increase rapidly in many societies, the risk of mismatch rises and the risk of diabetes may increase.

### *Refs:*

- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59
- Gluckman, P et al. Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*, 2008, 359:61-73
- Gluckman, P. et al. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proceedings of the Royal Society of London - Series B: Biological Sciences*, 2005, 272: 671-677
- Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull*, 2001, 60:5–20

## Developmental & environmental origins of adult disease



These hypotheses are based on impaired fetal nutrition and reductions in fetal growth. Size at birth serves as one of the markers of fetal nutrition and environment. Growth is only one indication of the environmental impact on the developing organism. Prematurity itself is another marker of an adverse uterine environment. There may be also responses of altered maturation and/or altered timing of fetal development, that do not show on size at birth. The fetus in an impaired environment has fewer options. These options can even include death. In less dramatic situations, the fetus can change its maturation, gestational length and/or growth rate. All these aspects play a role in inducing long-term consequences for those being born in a "mismatched" environment.

Prematurity is not a problem exclusive of the poor. Despite current levels of nutrition in developed countries, the nutrition of the fetus (and the infant) is often unbalanced because of tobacco smoke, unbalanced diets or because of the long and vulnerable fetal supply line.

Since the plastic period extends into the neonatal period, altered environments and altered nutrition in this period has long-term consequences. Rapid growth in childhood compensates for low birth weight. It is not known yet whether the catch-up phase is an independent risk factor or whether it is the biological/sociological (parental overfeeding) consequence of being a growth-impaired infant. However, compensatory growth can have high costs. In animals, their life-span is reduced. Barker's suggestion is that "a higher rate of cell division causes more rapid shortening of the protective ends of the chromosomes (telomeres) and hastens cell death and degradation. There are a number of other possible processes by which, in humans, undernutrition and small size at birth followed by rapid childhood growth could lead to cardiovascular disease, type 2 diabetes and hypertension in later life."

Nutrition is only one of the many factors that affect fetal development. There are environmental factors that have adverse consequences but have no effect on size at birth.

### Refs:

- Barker, DJP et al. Fetal origins of adult disease: strengths of effects and biological basis. *International Journal of Epidemiology*, 2002, 31:1235.
- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59
- WHO, FAO. Food safety and nutrition during pregnancy and infant feeding. *International Food safety Authorities Network*. 2008.

## Developmental & environmental origins of adult disease

### IMPLICATIONS OF THESE MODELS

- ❖ "Lifestyle" disease
- ❖ Improve maternal and child health
- ❖ More research needed in:
  - Genetic & epigenetic changes
  - Windows of opportunity during plasticity periods?
  - Peri-conception period
  - Father and mother's exposure
  - Women's nutrition
  - Metabolic, cardiovascular, skeletal & other systems



WHO

WHO

**BUT THE TIME FOR ACTION IS NOW**

10/19/2011

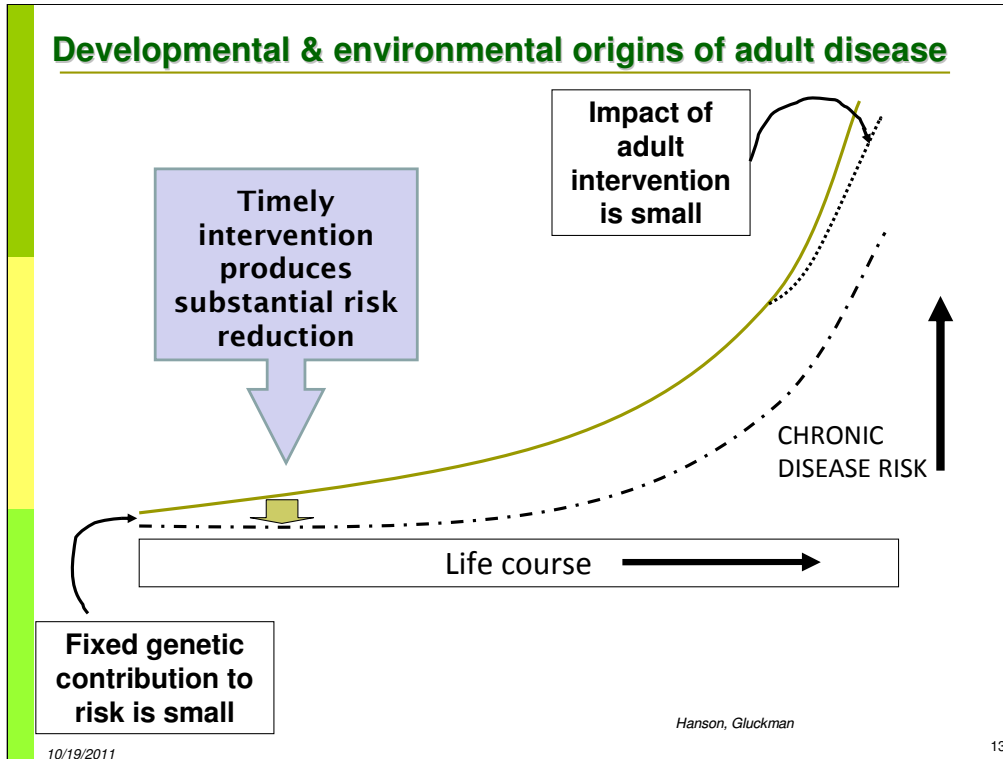
12

•The models we have presented may change our perspective about how to intervene in the epidemic "lifestyle" disease. Interventions on lifestyle only are just partially effective in those affected by inappropriate predictive adaptive responses. Improving maternal and fetal health will help us deal better with postnatal nutritional conditions.

•If the main programming mechanism is epigenetic change, then we must learn more about the changes that happen, their causes, the key nutrients involved and whether there are windows of opportunity during which the effects can be reverted. Regarding certain changes, like the reduction of the number of nephrons, only preventive measures can be taken.

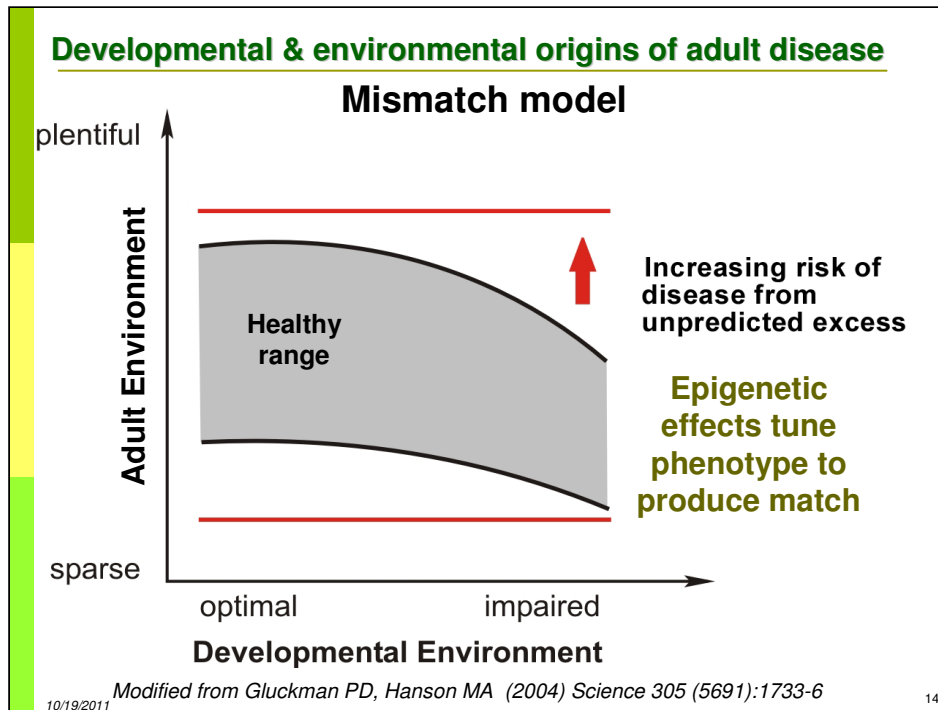
•As we mentioned, the periconceptual period is important, that is why we should concentrate on women's nutrition during conception and during early pregnancy. However, we don't know yet what is the best diet for women during the different stages of their life and during pregnancy.

•Even though initially, focus was on the metabolic system, similar arguments are beginning to be studied about cardiovascular and skeletal changes, necessary for reproduction and survival. The adaptive responses model is also applicable to other programmed physiological systems.



As shown in this chart by Dr. M Hanson and Dr. P Gluckman, the interventions that produce substantial risk reduction of the risk of chronic disease may need to occur at critical periods early in the life course, eventually even before conception, before the genetic determinants of the risk of developing metabolic disease are defined.

*Image kindly provided by Dr. M. Hanson, Dr. P. Gluckman.*

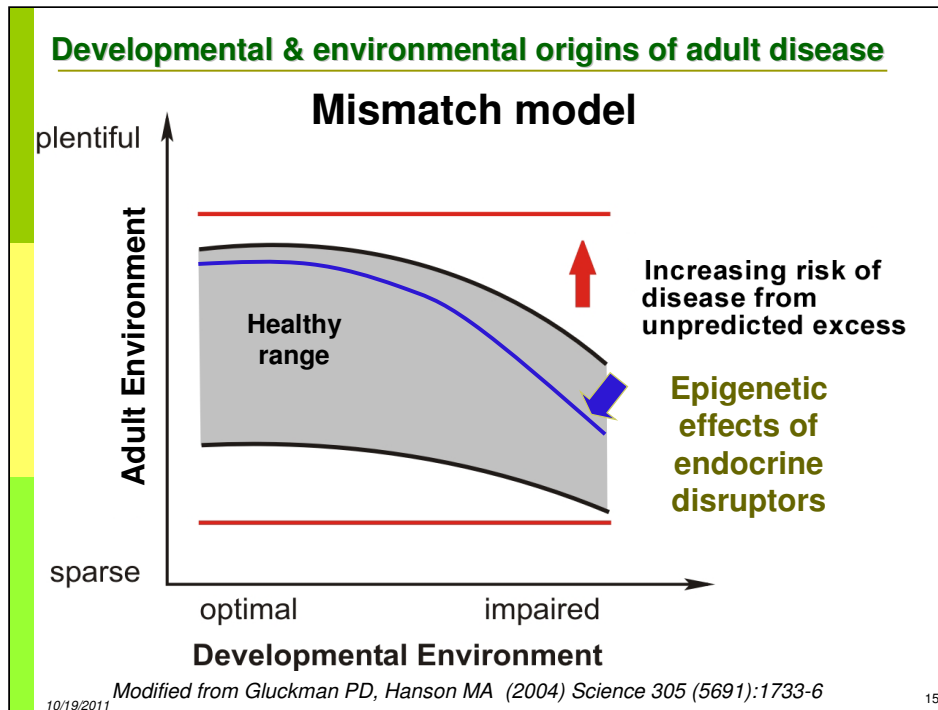


The relationship between adult and developmental nutritional environment is shown. The shaded area is the zone of appropriate predictive adaptive responses (healthy range). The risk of disease in relation to nutrition excess increases as the developmental environment is compromised (as shown by red arrow).

*Refs:*

- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59
- Gluckman P, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science*, 2004, 305 (5691):1733-6

*Image modified from Gluckman P, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science, 2004, 305 (5691):1733-6. Image kindly provided by Dr. M. Hanson, Dr. P. Gluckman.*



As we can see in the image, the risk of disease from unpredicted nutritional excess is increased if we take into account the epigenetic effects of endocrine disruptors.

*Refs:*

- Gluckman, P. et al. The fetal, neonatal, and infant environments - the long-term consequences for disease risk. *Early Human Development*, 2005, 81: 51-59
- Gluckman P, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science*, 2004, 305 (5691):1733-6
- Grandjean P, ed. Prenatal programming toxicity. *Basic and Clinical Pharmacology and Toxicology*. 2008, 102 (2).
- Schwartz JM, Woodruff TJ. Shaping our legacy: reproductive health and the environment. *University of California, San Francisco*. Program on Reproductive Health and the Environment. 2008.

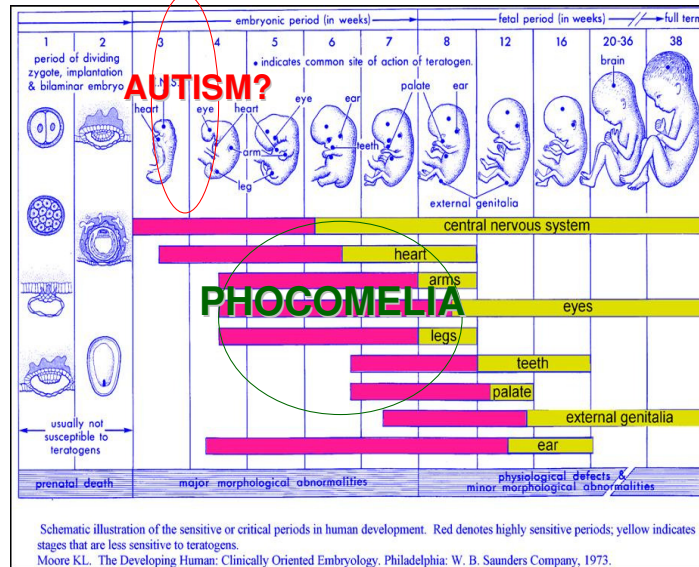
*Image modified from Gluckman P, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science, 2004, 305 (5691):1733-6. Image kindly provided by Dr. M. Hanson, Dr. P. Gluckman.*

<<NOTE TO USER: For more information see module on endocrine disruptors.>>

## Developmental & environmental origins of adult disease

### DYNAMIC DEVELOPMENTAL PHYSIOLOGY

#### WINDOWS OF DEVELOPMENT



10/19/2011

Moore, Elsevier Inc, 1973

16

Physiological differences manifest in more ways than immature metabolic pathways. Because important systems are still differentiating and growing, the fetus and then the child, has unique susceptibilities compared to adults — and critical time windows in those susceptibilities.

- Preconception
- Gestation
  - thalidomide, diethylstilbestrol (DES)
  - ionizing radiation
  - methylmercury
  - second-hand tobacco smoke
  - lead.

There has been an explosion of knowledge about development in past decade or so, and it is hard to remember that it was only about 50 years ago that the discovery was made that the fetus is vulnerable to exposures. The phocomelia epidemic resulting from use of thalidomide in pregnancy was an early and dramatic example of the ability of chemicals to cross the placenta and damage the fetus. Additionally, thalidomide administered during a small, 4-day window between gestational days 20 and 24, may increase the risk of autism (Stromland, 1994). More than one system can be susceptible and different pathology may occur depending upon the dose and timing of exposure.

Now we know that other exposures during gestation can harm systems, and some are listed here. We also know that preconception exposure of both parents can cause harm to children, as well as postnatal exposures.

<<NOTES TO USER: It is important to point out the different responses to insults shown on the bottom bar of the figure. Significant insult during the embryonic phase will result in pregnancy loss (first 2 weeks) or major organ malformation. During the fetal stage, damage is more subtle and related to system dysfunction.>>

Ref:

•Stromland K et al. Autism in thalidomide embryopathy: a population study, *Developmental Medicine & Child Neurology*, 1994, 36(4):351.  
*Of a population of 100 Swedish thalidomide embryopathy cases, at least four met full criteria for DSM-III-R autistic disorder and ICD-10 childhood autism. Thalidomide embryopathy of the kind encountered in these cases affects fetal development early in pregnancy, probably on days 20 to 24 after conception. It is argued that the possible association of thalidomide embryopathy with autism may shed some light on the issue of which neural circuitries may be involved in autism pathogenesis.*

Figure: Reprinted from *The developing human*, Moore, Elsevier Inc., 1973. Used with copyright permission (2004) from Elsevier.

## Developmental & environmental origins of adult disease

### **PHYSIOLOGICAL & TOXICOKINETIC CHANGES DURING PREGNANCY**

<b>Absorption</b>	<b>Physiological change</b>	<b>Toxicokinetic change</b>
Gastric emptying time	Increased	Absorption increased
Intestinal motility	Decreased	Absorption increased
Pulmonary function	Increased	Pulmonary exposure increased
Cardiac output	Increased	Absorption increased
Blood flow to skin	Increased	Absorption increased
Dermal hydration	Increased	Absorption +/-

*Selevan et al, 2005. Modified from Silvaggio & Mattison*

10/19/2011

17

*Exposure issues vary according to the time at which they occur: before conception, prenatally, or postnatally. The preconceptional exposures of concern may occur acutely prior to conception or result from an increased body burden in either parent accumulated over a long period of exposure. Prenatally, exposures often change throughout pregnancy, e.g. if a woman reduces her alcohol consumption, quits smoking, or avoids using medicines. In addition to these variations, the altered absorption, distribution, metabolism, and excretion of chemicals during pregnancy result in changes in internal dosing.*

#### *Refs and image sources:*

- Selevan SG, Kimmel CA, Mendola P. Windows of susceptibility to environmental exposures in children. In: *Children's health and the environment: a global perspective*. Pronczuk J, ed. WHO, Geneva, 2005, 2:17-25.
- Silvaggio T, Mattison DR. Comparative approach to toxicokinetics. In: Paul M, ed. *Occupational and environmental reproductive hazards: a guide for clinicians*. Baltimore, MD, Williams & Wilkins, 1993:25–36.

## Developmental & environmental origins of adult disease

### **PHYSIOLOGICAL & TOXICOKINETIC CHANGES DURING PREGNANCY**

<b>Absorption</b>	<b>Physiological change</b>	<b>Toxicokinetic change</b>
<b>Metabolism</b>		
Hepatic metabolism	+/-	Metabolism +/-
Extrahepatic metabolism	+/-	Metabolism +/-
Plasma proteins	Decreased	Metabolism +/-
<b>Excretion</b>		
Renal blood flow	Increased	Increased renal elimination
Glomerular filtration rate	Increased	Increased renal elimination
Pulmonary function	Increased	Increased pulmonary elimination
Plasma proteins	Decreased	Elimination +/-

*Selevan et al, 2005. Modified from Silvaggio & Mattison*

10/19/2011

18

*Exposure issues vary according to the time at which they occur: before conception, prenatally, or postnatally. The preconceptional exposures of concern may occur acutely prior to conception or result from an increased body burden in either parent accumulated over a long period of exposure. Prenatally, exposures often change throughout pregnancy, e.g. if a woman reduces her alcohol consumption, quits smoking, or avoids using medicines. In addition to these variations, the altered absorption, distribution, metabolism, and excretion of chemicals during pregnancy result in changes in internal dosing.*

#### *Refs and image sources:*

- Selevan SG, Kimmel CA, Mendola P. Windows of susceptibility to environmental exposures in children. In: *Children's health and the environment: a global perspective*. Pronczuk J, ed. WHO, Geneva, 2005, 2:17-25.
- Silvaggio T, Mattison DR. Comparative approach to toxicokinetics. In: Paul M, ed. *Occupational and environmental reproductive hazards: a guide for clinicians*. Baltimore, MD, Williams & Wilkins, 1993:25–36.

## Developmental & environmental origins of adult disease

### DEVELOPMENTAL TOXICANTS

#### Demonstrated:

- ❖ Methyl mercury
- ❖ Lead
- ❖ Ionizing radiations
- ❖ Polychlorinated biphenyls
- ❖ Polycyclic aromatic hydrocarbons
- ❖ Fine particulate matters
- ❖ Second-hand tobacco smoke

#### Highly Suspected:

- ❖ Organic solvents
- ❖ Some pesticides
- ❖ Some air contaminants
- ❖ Others...

#### Developmental toxicants' effects:

- Spontaneous abortion
- Stillbirth
- Low Birth weight
- Decreased head circumference
- Preterm delivery
- Birth defects
- Visual and hearing deficits
- Chromosomal abnormalities
- Intellectual deficits
- Others

10/19/2011

19

Developmental toxicants are agents that adversely affect the developing embryo or fetus. Some mothers may be exposed to these in the occupational setting. In addition to highly sensitive windows for morphological abnormalities (birth defects), there are also time windows important for the development of physiological defects and morphological changes at the tissue, cellular and subcellular levels. Most existing data are related to preconceptional and prenatal exposures. Data on prenatal exposures are based mainly on studies of maternal exposure to pharmaceuticals (e.g., diethylstilbestrol, thalidomide) and parental alcohol use, smoking, and occupational exposures. Information on critical windows for exposure during the postnatal period is scarce. Postnatal exposures have been examined in detail for only a few environmental agents, including lead, mercury, some pesticides, and radiation. Developmental exposures may result in health effects observed:

- prenatally and at birth, such as spontaneous abortion, stillbirth, low birth weight, small size for gestational age, infant mortality, and malformation;
- in childhood, such as asthma, cancer, neurological and behavioural effects;
- at puberty, such as alterations in normal development and impaired reproductive capacity;
- in adults, such as cancer, heart disease, and degenerative neurological and behavioural disorders.

Fetal exposures are "parenteral", integrated exposures from the mother's total exposures.

<<NOTE TO USER: For more information see module on occupational exposures and child health.>>

#### Refs:

- Birnbaum L. The effects of environmental chemicals on human health. *Fertility and Sterility*, 2008, 89(1):e31
- Blanck HM et al. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. *Epidemiology*, 2000, 11(6):641-7.
- CPCHE. Child health and the environment, a primer. *CPCHE*, 2005.
- Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. *Environmental health perspectives*, 1997, 105(10):1068-77.
- Gonzalez-Cossio T et al H. Decrease in birth weight in relation to maternal bonelead burden. *Pediatrics*, 1997, 100(5):856-62.
- Hu FB et al. Prevalence of asthma and wheezing in public schoolchildren: association with maternal smoking during pregnancy. *Annals of allergy, asthma and immunology*, 1997, 79(1):80-4.
- Krstevska-Konstantinova M et al. Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides. *Human reproduction*, 2001, 16(5):1020-6.
- Mendola P. et al. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. *Fertility and Sterility*, 2008, 89 (1):e81-e94.
- Miller RW. Special susceptibility of the child to certain radiation-induced cancers. *Environmental health perspectives*, 103(Suppl. 6):41-4.
- Moore KL, Persaud TVN. The developing human: clinically oriented embryology. W.B. Saunders, Philadelphia, 1973, 98.
- Needleman HL et al. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *New England journal of medicine*, 1990, 322:83-8.
- Osmond C et al. Early growth and death from cardiovascular disease in women. *British medical journal*, 1993.
- Selevan SG, Kimmel CA, Mendola P. Windows of susceptibility to environmental exposures in children. In: *Children's health and the environment: a global perspective*. Pronczuk J, ed. WHO, Geneva, 2005, 2:17-25
- Selevan SG, Lemasters GK. The dose-response fallacy in human reproductive studies of toxic exposures. *Journal of occupational medicine*, 1987, 29(5):451-4.
- Wadsworth ME, Kuh DJ. Childhood influences on adult health: a review of recent work from the British 1946 national birth cohort study, the MRC National Survey of Health and Development. *Paediatric and perinatal epidemiology*, 1997, 11:2-20.

## Developmental & environmental origins of adult disease

### WINDOWS OF DEVELOPMENT: FATHERS AND THEIR OFFSPRING

- ❖ Paternal exposure to: Mercury, ethylene oxide, rubber chemicals, solvents, linked to spontaneous abortion
- ❖ Paternal occupation: Painters – anencephaly  
(Brender. *Am J Epidemiol*, 1990, 131(3):517)  
Mechanics, welders – Wilms tumour  
(Olshan. *Cancer Res*, 1990, 50(11):3212)  
Textiles – stillbirth, pre-term delivery  
(Savitz. *Am J Epidemiol*, 1989, 129(6):1201)

Possible mechanism: impairment of a paternal gene required for the normal growth and development of the fetus

*“The special and unique vulnerability of children to environmental hazards” Bearer, Neurotoxicology, 2000, 21(6):925*

10/19/2011

20

Preconception paternal exposures are now increasingly recognized as important to the health and development of the fetus.

Such exposures may increase the chance of certain diseases or adverse pregnancy outcomes as seen in the offspring. This is supported by research in animals and may well have a genetic or epigenetic mechanism.

<<READ SLIDE.>>

<<NOTE TO USER: you may want to stress exposures/occupations that are regionally specific if there are data to support prenatal or preconception effects. You may refer to the Occupational exposure module or the Male reproductive health modules for further information.>>

Refs:

•Bearer CF. The special and unique vulnerability of children to environmental hazards. *Neurotoxicology*, 2000, 21:925-34.

•Brender JD. Paternal occupation and anencephaly. *Am J Epidemiol*, 1990, 131:517-21.

•Olshan AF et al. Wilms' tumor and paternal occupation. *Cancer Res*, 1990, 50:3212.

*A case-control study was conducted to examine the relationship between Wilms' tumour and paternal occupational exposures. The case group consisted of 200 children diagnosed as having Wilms' tumour who were registered at selected National Wilms' Tumour Study institutions during the period 1 June, 1984, to 31 May, 1986. Disease-free controls were matched to each case using a random digit dialling procedure. The parents of cases and controls completed a self-administered questionnaire. There was no consistent pattern of increased risk for paternal occupational exposure to hydrocarbons or lead found in this study. However, certain paternal occupations were found to have an elevated odds ratio (OR) of Wilms' tumour, including vehicle mechanics, auto body repairmen, and welders. Offspring of fathers who were auto mechanics had a 4- to 7-fold increased risk of Wilms' tumour for all three time periods. The largest increased odds ratio for auto mechanics was in the preconception period [OR = 7.58; 95% confidence interval (CI) = 0.90-63.9]. Welders had a 4- to 8-fold increased odds ratio, with the strongest association during pregnancy (OR = 8.22; CI = 0.95-71.3). Although chance cannot be excluded as a possible explanation, association of Wilms' tumour with these occupations has been reported in previous studies. Further study is needed to provide data on the specific occupational exposures involved.*

•Savitz DA et al. Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol*, 1989, 129:1201-18.

## **Developmental & environmental origins of adult disease**

### **EXAMPLE OF AN INORGANIC CHEMICAL ARSENIC (As)**

- ❖ **From natural erosion, pesticide run-off, coal burning, smelting, glass and electronic production waste**
- ❖ **Skin lesions and cancer, vascular and neurological disease, increased risk of cancer**
- ❖ **WHO guideline: 0.01 mg/L (ppm)**
- ❖ **Arsenic crosses the placenta**
- ❖ **Previous studies: *in utero* exposure to arsenic linked to increased risk for stillbirth, and spontaneous abortion**

10/19/2011

21

Arsenic is a naturally occurring element, which can be introduced into water through the dissolution of minerals, from industrial effluent (drainage from goldmines) and from atmospheric deposition (burning of fossil fuels and wastes). These sources make significant contributions to the arsenic concentrations in drinking-water and may be harmful to health. The body rapidly excretes organic forms of arsenic, and it is the inorganic trivalent form that is of most concern.

Although concentrations in natural water are generally less than 0.005 mg/litre, some countries have reported very high concentrations, particularly in groundwater supplies. In Bangladesh, for example, over 25 000 wells are contaminated with arsenic at levels above 0.05 mg/litre. Food is also a significant source of arsenic, but usually in highly complex forms that are biologically unavailable and essentially non-toxic.

Although studies indicate that arsenic may be essential for some animal species, there is no indication that it is essential for humans.

Arsenic compounds are readily absorbed by the gastrointestinal tract, and then bind to haemoglobin and are deposited in the liver, kidneys, lungs, spleen and skin. Inorganic arsenic does not appear to cross the blood-brain barrier, but can cross the placenta.

Approximately 45–85% of ingested arsenic is excreted in the urine within 1–3 days.

The major health effects are caused by chronic exposure to low levels from the consumption of arsenic-contaminated water. A number of studies in Bangladesh and West Bengal have documented the effects of consuming water containing elevated concentrations of arsenic (> 0.3 mg/litre). Consumption over periods of 5–25 years was reported to produce skin lesions, skin cancer, vascular disease, effects on the nervous system and possibly cancer of other organs.

The only available treatment for chronic arsenic poisoning is to remove the patient from the source of exposure and provide supportive care.

#### *Refs:*

•ATSDR. Arsenic toxicity. Case Studies in Environmental Medicine, No. 5. US Department of Health and Human Services, Atlanta, GA, *Agency of Toxic Substances and Disease Registry*, 1990

•International Programme on Chemical Safety. Environmental Health Criteria No. 18. Arsenic. *World Health Organization*, Geneva, 1981.

•United Nations Synthesis Report on Arsenic in Drinking Water. Available at [www.who.int/water\\_sanitation\\_health/dwq/arsenic3/en/print.html](http://www.who.int/water_sanitation_health/dwq/arsenic3/en/print.html) - accessed August 2008.

## Developmental & environmental origins of adult disease

### EXAMPLE: ARSENIC AND THE ANTOFAGASTA STUDY

- ❖ High arsenic exposure in Antofagasta (Chile) from 1958 to 1970
  - ❖ Study of exposed children (1958 – 1971): Increase in mortality from lung cancer and bronchiectasis when *in utero* + childhood exposure to arsenic in drinking water
- |                       |                                     |
|-----------------------|-------------------------------------|
| - Exposure in:        |                                     |
| Early childhood       | <i>In utero and early childhood</i> |
| - Mortality due to:   |                                     |
| cancer SMR=7          | SMR=6.1                             |
| bronchiectasis SMR=12 | SMR=46.2                            |

10/19/2011

SMR: standardized mortality ratios

22

<<READ SLIDE.>>

Ref:

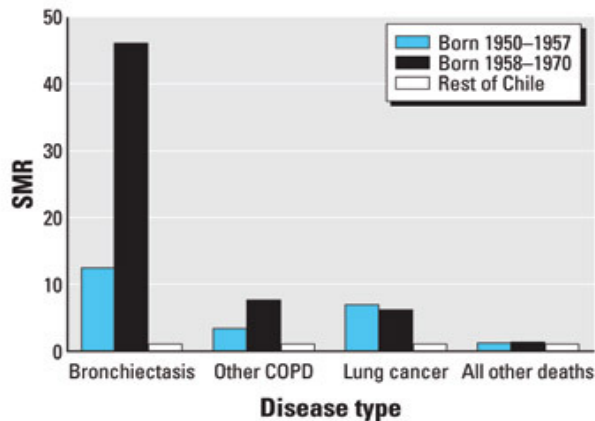
•Smith A et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *EHP*, 2006,114 (8):1293-1296 .

*Arsenic in drinking water is an established cause of lung cancer, and preliminary evidence suggests that ingested arsenic may also cause nonmalignant lung disease. Antofagasta is the second largest city in Chile and had a distinct period of very high arsenic exposure that began in 1958 and lasted until 1971, when an arsenic removal plant was installed. This unique exposure scenario provides a rare opportunity to investigate the long-term mortality impact of early-life arsenic exposure. In this study, we compared mortality rates in Antofagasta in the period 1989–2000 with those of the rest of Chile, focusing on subjects who were born during or just before the peak exposure period and who were 30–49 years of age at the time of death. For the birth cohort born just before the high-exposure period (1950–1957) and exposed in early childhood, the standardized mortality ratio (SMR) for lung cancer was 7.0 [95% confidence interval (CI) , 5.4–8.9 ;  $p < 0.001$ ] and the SMR for bronchiectasis was 12.4 (95% CI, 3.3–31.7 ;  $p < 0.001$ ) . For those born during the high-exposure period (1958–1970) with probable exposure in utero and early childhood, the corresponding SMRs were 6.1 (95% CI, 3.5–9.9 ;  $p < 0.001$ ) for lung cancer and 46.2 (95% CI, 21.1–87.7 ;  $p < 0.001$ ) for bronchiectasis. These findings suggest that exposure to arsenic in drinking water during early childhood or in utero has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and nonmalignant lung disease.*

SMR: standardized mortality ratios

## Developmental & environmental origins of adult disease

Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in *utero* and in early childhood



COPD SMRs for Antofagasta/Mejillones for individuals 30-49 years of age, pooled.

Smith A et al *Environ Health Perspectives*, 2006 114:1293-6

10/19/2011

23

**Exposure to arsenic in drinking water during early childhood or in utero has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and nonmalignant lung disease.**

Exposure to arsenic in drinking water during early childhood or in utero has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and nonmalignant lung disease.

<<READ SLIDE.>>

Ref:

•Smith A et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *EHP*, 2006,114 (8):1293-1296 .

*Arsenic in drinking water is an established cause of lung cancer, and preliminary evidence suggests that ingested arsenic may also cause nonmalignant lung disease. Antofagasta is the second largest city in Chile and had a distinct period of very high arsenic exposure that began in 1958 and lasted until 1971, when an arsenic removal plant was installed. This unique exposure scenario provides a rare opportunity to investigate the long-term mortality impact of early-life arsenic exposure. In this study, we compared mortality rates in Antofagasta in the period 1989-2000 with those of the rest of Chile, focusing on subjects who were born during or just before the peak exposure period and who were 30-49 years of age at the time of death. For the birth cohort born just before the high-exposure period (1950-1957) and exposed in early childhood, the standardized mortality ratio (SMR) for lung cancer was 7.0 [95% confidence interval (CI) , 5.4-8.9 ;  $p < 0.001$ ] and the SMR for bronchiectasis was 12.4 (95% CI, 3.3-31.7 ;  $p < 0.001$ ) . For those born during the high-exposure period (1958-1970) with probable exposure in utero and early childhood, the corresponding SMRs were 6.1 (95% CI, 3.5-9.9 ;  $p < 0.001$ ) for lung cancer and 46.2 (95% CI, 21.1-87.7 ;  $p < 0.001$ ) for bronchiectasis. These findings suggest that exposure to arsenic in drinking water during early childhood or in utero has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and nonmalignant lung disease.*

Image from Smith A et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *EHP*, 2006,114 (8):1293-1296 .Copyright notice: This is an Open Access article. doi:10.1289/ehp.8832

SMR: standardized mortality ratios

## **Developmental & environmental origins of adult disease**

### **EXAMPLE: TOBACCO SMOKE**

❖ **Lung development is a multi-event process that begins at the first month of gestation and continues postnatally.**

- Toxicants to developing lungs: second-hand tobacco smoke, bioactivated compounds and oxidant gases
- Targets: epithelial cells that are maturing and/or proliferating

❖ **Developing fetus more susceptible than adult to polycyclic aromatic hydrocarbons carcinogenicity:**

- Increased susceptibility of the fetus to DNA damage
- Reduced ability to clear second-hand tobacco smoke constituents

❖ **Tobacco metabolites in the fetus: toxic effects.**

10/19/2011

24

<<READ SLIDE>>

*Refs:*

•Jaakkola JJ, Jaakkola N, Zahlsen K. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration, *EHP*, 2001, 109 (6): 557

•Perera FP et al. Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage. *Environ Health Perspect*, 2004, 112(10):1133-6.

•Pinkerton KE, Joad JP. The mammalian respiratory system and critical windows of exposure for children's health, *EHP*, 2000, 108 (S3):457.

*PAHs: polycyclic aromatic compounds*

*SHS: second hand tobacco smoke*

## Developmental & environmental origins of adult disease

### EXAMPLE: TOBACCO SMOKE

- ❖ **Maternal smoking is risk factor for:**
  - low lung function, low birth weight, pre-term delivery, sudden death, lower respiratory illness, wheezing and asthma in children, debilitating asthma, obstructive pulmonary disease, cancer in adults.**
- ❖ **Increased susceptibility of the fetus to DNA damage and reduced ability to clear tobacco constituents**
- ❖ **Effects on lung development:**
  - Diminishing airway and alveolar growth
  - Structural alterations
  - Interference with control of respiration and developing immune system
  - Reduction in fetal breathing movements: exposure to hypoxia even 1 hr after cigarette was smoked
  - Changes in CNS sensitivity to blood gases = impaired control of breathing
  - Reduced placental blood flow, reduced supply of nutrients and oxygen to the fetus and growth retardation: **Fetal origins of disease**

10/19/2011

25

Maternal smoking is risk factor for a long list of adverse outcome in the child and adult.

Tobacco particles have multiple effects on lung development. Lung development continues several years after birth, so exposures after birth are still affecting lung development, structurally and functionally.

<<NOTE TO USER: For more information see modules on second hand smoke and indoor air pollution.>>

Refs:

•Hoo AH et al. Respiratory function among preterm infants whose mothers smoked during pregnancy. *American Journal of Respiratory and Critical Care Medicine*, 1998, 158 (3):700.

*In conclusion, the findings of this study suggest that, in infants of mothers who smoke during pregnancy, changes in respiratory function are evident by at least 7 wk prior to the expected date of delivery. At the time of testing, none of these infants had been exposed to tobacco smoke postnatally. However, many had been heavily exposed in utero as reflected by infant urinary cotinine levels at birth of a magnitude comparable to that reported in active smokers. Thus, prenatal exposure to tobacco has adverse effects that are evident some 2 mo before most babies are born. Because diminished respiratory function in very early life has been shown to precede and predict wheezing lower respiratory illnesses in early childhood, it is likely that these infants are also at increased risk of such illnesses. This would suggest that the incidence and severity of respiratory illnesses in preterm infants might be diminished by programs to reduce the prevalence of maternal smoking in pregnancy. These findings highlight the need to identify effective strategies to help women stop smoking.*

•Yeatts K et al. A brief targeted review of susceptibility factors, environmental exposures, asthma incidence and recommendations for future asthma incidence research. *EHP*, 2006, 114 (4):634

•Perera FP et al. Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage. *Environ Health Perspect*, 2004, 112(10):1133-6.

*Polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene (BaP) are widespread air contaminants released by transportation vehicles, power generation, and other combustion sources. Experimental evidence indicates that the developing fetus is more susceptible than the adult to carcinogenic effects of PAHs, although laboratory studies in rodents suggest that the dose to fetal tissues is an order of magnitude lower than that to maternal tissues. To assess fetal versus adult susceptibility to PAHs and environmental tobacco smoke (ETS), we compared carcinogen-DNA adducts (a biomarker associated with increased cancer risk) and cotinine (a biomarker of tobacco smoke exposure) in paired blood samples collected from mothers and newborns in New York City. We enrolled 265 nonsmoker African-American and Latina mother-newborn pairs in New York City between 1997 and 2001 (estimated average ambient air BaP concentrations < 0.5 ng/m<sup>3</sup>). Despite the estimated 10-fold lower fetal dose, mean levels of BaP-DNA adducts as determined by high-performance liquid chromatography-fluorescence were comparable in paired New York City newborn and maternal samples (0.24 adducts per 10(8) nucleotides, 45% of newborns with detectable adducts vs. 0.22 per 10(8) nucleotides, 41% of mothers with detectable adducts). However, by the Wilcoxon signed-rank test, the levels in newborns were higher (p = 0.02). Mean cotinine was higher in newborns than in mothers (1.7 ng/mL, 47% detectable vs. 1.28 ng/mL, 44% detectable). Consistent with our prior study in a Caucasian Polish population, these results indicate increased susceptibility of the fetus to DNA damage and reduced ability to clear ETS constituents. The findings have implications for risk assessment, given the need to protect children as a sensitive subset of the population.*

## Developmental & environmental origins of adult disease

### EXAMPLE: TOBACCO SMOKE

- ❖ **Secondhand smoke + urban air pollutants:**
  - Effect greater than the sum of individual effects
  - Reduced fetal growth, lower birth weight
  - Problems in learning and school performance
- ❖ **Women who quit smoking during pregnancy and who are exposed to second-hand smoke: babies born with more gene mutations (umbilical cord blood studies)**
- ❖ **High doses of vitamin C can be beneficial**

10/19/2011

26

<<READ SLIDE>>

<<NOTE TO USER: For more information see module on second hand smoke.>>

Refs:

•Dejmek J et al. The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth, *EHP*, 2002, 110 (6):601

*We can conclude that, in accordance with current knowledge, ETS exposure significantly reduced the BW of infants delivered by nonsmoking women. The present study also showed that ETS exposure increases the adverse effects of active smoking. Thus, ETS contributed to BW reduction in babies of AS mothers. The exposure to ETS increased the risk of LBW infants not only for nonsmoking but also for AS mothers. We found a similar relationship between IUGR risk and ETS exposure only as an additional risk in AS mothers. The adjusted relative risk of IUGR in ETS-exposed nonsmoking mothers was not different from unity. The impact of active smoking during pregnancy on BW was much stronger than the impact of similar levels of smoking before (and during early) pregnancy. It appears that the impact of active and/or passive smoking on fetal growth increases with the duration of exposure during pregnancy. This observation shows the usefulness of programs encouraging smoking cessation during pregnancy. The presented results support the presumption that ETS exposure during pregnancy represents an important factor that can endanger fetal development and increase the prevalence of adverse birth outcomes. Our results suggest that about 8% of all neonates with LBW born in the Czech Republic may be attributed to ETS exposure of nonsmoking mothers. Another portion of LBW births, although slightly smaller, may be due to the ETS exposure of smoking women. Grant SG. Qualitatively and quantitatively similar effects of active and passive maternal tobacco smoke exposure on in utero mutagenesis at the HPRT locus. *BMC Pediatrics*, 2005, 5: 20.*

•Proskocil BJ et al. Vitamin C prevents the effects of prenatal nicotine on pulmonary function in newborn monkeys. *Am J Respir Crit Care Med*, 2005, 171(9):1032

*Smoking during pregnancy leads to decreased pulmonary function and increased respiratory illness in offspring. Our laboratory has previously demonstrated that many effects of smoking during pregnancy are mediated by nicotine. We now report that vitamin C supplementation can prevent some of the effects of maternal nicotine exposure on pulmonary function of offspring. Timed-pregnant rhesus monkeys were treated with 2 mg/kg/day nicotine bitartrate from Gestation Days 26 to 160. On Gestation Day 160 (term, 165 days) fetuses were delivered by C-section and subjected to pulmonary function testing the following day. Nicotine exposure significantly reduced forced expiratory flows, but supplementation of mothers with 250 mg vitamin C per day prevented the effects of nicotine on expiratory flows. Vitamin C supplementation also prevented the nicotine-induced increases in surfactant apoprotein-B protein. Neither nicotine nor nicotine plus vitamin C significantly affected levels of cortisol or cytokines, which have been shown to affect lung development and surfactant expression. Prenatal nicotine exposure significantly decreased levels of elastin content in the lungs of offspring, and these effects were slightly attenuated by vitamin C. These findings suggest that vitamin C supplementation may potentially be clinically useful to limit the deleterious effects of maternal smoking during pregnancy on offspring's lung function.*

•Perera FP et al. Molecular evidence of an interaction between prenatal environmental exposures and birth outcomes in a multiethnic population. *Environ Health Perspectives*, 2004, 112 (5):626.

## Developmental & environmental origins of adult disease

### **EXAMPLE: TOBACCO SMOKE & AIR POLLUTION**

Fetal exposure to polycyclic aromatic hydrocarbons linked to babies that are small at birth for their gestational age (SGA)

Women who smoke during pregnancy: *Polycyclic aromatic hydrocarbons and carbon monoxide linked to a 200 g decrease in birth weight.*

Pregnant women exposed to high polycyclic aromatic hydrocarbons near the World Trade Center on 9/11 and after had smaller babies.

Lederman et al

*Effects of the World Trade Center event on birth outcomes EHP, 2004.*

10/19/2011

27

<<READ SLIDE.>>

Refs:

•Lederman SA et al. The effects of the World Trade Center event on birth outcomes among term deliveries at three lower Manhattan hospitals. *Environ Health Perspect.* 2004, 112(17):1772-8.

*The effects of prenatal exposure to pollutants from the World Trade Center (WTC) disaster on fetal growth and subsequent health and development of exposed children remain a source of concern. We assessed the impact of gestational timing of the disaster and distance from the WTC in the 4 weeks after 11 September on the birth outcomes of 300 nonsmoking women who were pregnant at the time of the event. They were recruited at delivery between December 2001 and June 2002 from three hospitals close to the WTC site. Residential and work addresses of all participants for each of the 4 weeks after 11 September 2001 were geocoded for classification by place and timing of exposure. Average daily hours spent at each location were based on the women's reports for each week. Biomedical pregnancy and delivery data extracted from the medical records of each mother and newborn included medical complications, type of delivery, length of gestation, birth weight, birth length, and head circumference. Term infants born to women who were pregnant on 11 September 2001 and who were living within a 2-mile radius of the WTC during the month after the event showed significant decrements in term birth weight (-149 g) and birth length (-0.82 cm), compared with infants born to the other pregnant women studied, after controlling for sociodemographic and biomedical risk factors. The decrements remained significant with adjustment for gestational duration (-122 g and -0.74 cm, respectively). Women in the first trimester of pregnancy at the time of the WTC event delivered infants with significantly shorter gestation (-3.6 days) and a smaller head circumference (-0.48 cm), compared with women at later stages of pregnancy, regardless of the distance of their residence or work sites from the WTC. The observed adverse effects suggest an impact of pollutants and/or stress related to the WTC disaster and have implications for the health and development of exposed children.*

•Witschi H. et al. The toxicology of environmental tobacco smoke. *Annu. Rev. Pharmacol. Toxicol.* 1997, 37:29-52

## Developmental & environmental origins of adult disease

### AIR POLLUTION AND ASTHMA

- ❖ Canadian population-based nested case control study on exposure to ambient air pollution *in utero* and during the first year of life & risk of asthma (n=37,401)
- ❖ Increased risk of asthma with increased early life exposure to CO, NO, NO<sub>2</sub>, PM<sub>10</sub>, SO<sub>2</sub>, and black carbon and proximity to point sources
- ❖ Traffic-related pollutants were associated with the highest risks
- ❖ Early childhood exposure to air pollutants found to play a role in development of asthma

Clark et al, *Environ Health Perspectives*, 2009

10/19/2011

28

<<READ SLIDE.>>

Ref:

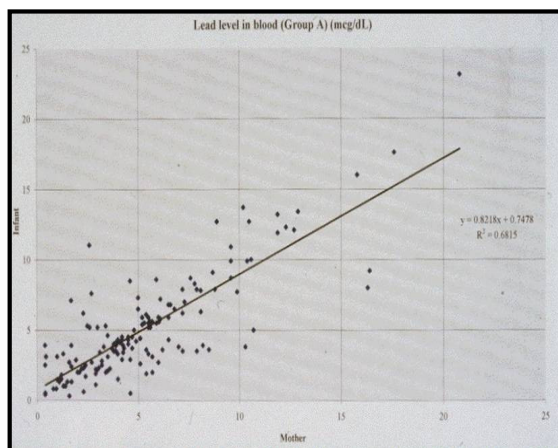
•Clark NA et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect*, 2009, 118(2)

*Background: There is increasing recognition of the importance of early environmental exposures in the development of childhood asthma. Outdoor air pollution is a recognized asthma trigger, but it is unclear whether exposure influences incident disease. We investigated the effect of exposure to ambient air pollution in utero and during the first year of life on risk of subsequent asthma diagnosis in a population-based nested case control study. Methods: We assessed all children born in southwestern British Columbia in 1999 and 2000 (n = 37,401) for incidence of asthma diagnosis up to 3–4 years of age using outpatient and hospitalization records. Asthma cases were age- and sex-matched to five randomly chosen controls from the eligible cohort. We estimated each individual's exposure to ambient air pollution for the gestational period and first year of life using high-resolution pollution surfaces derived from regulatory monitoring data as well as land use regression models adjusted for temporal variation. We used logistic regression analyses to estimate effects of carbon monoxide, nitric oxide, nitrogen dioxide, particulate matter  $\leq 10 \mu\text{m}$  and  $\leq 2.5 \mu\text{m}$  in aerodynamic diameter (PM<sub>10</sub> and PM<sub>2.5</sub>), ozone, sulfur dioxide, black carbon, wood smoke, and proximity to roads and point sources on asthma diagnosis. Results: A total of 3,482 children (9%) were classified as asthma cases. We observed a statistically significantly increased risk of asthma diagnosis with increased early life exposure to CO, NO, NO<sub>2</sub>, PM<sub>10</sub>, SO<sub>2</sub>, and black carbon and proximity to point sources. Traffic-related pollutants were associated with the highest risks: adjusted odds ratio = 1.08 (95% confidence interval, 1.041.12) for a 10- $\mu\text{g}/\text{m}^3$  increase of NO, 1.12 (1.071.17) for a 10- $\mu\text{g}/\text{m}^3$  increase in NO<sub>2</sub>, and 1.10 (1.061.13) for a 100- $\mu\text{g}/\text{m}^3$  increase in CO. These data support the hypothesis that early childhood exposure to air pollutants plays a role in development of asthma.*

## Developmental & environmental origins of adult disease

### EXAMPLE: LEAD & PRENATAL ROUTES OF EXPOSURE

- ❖ Lead crosses the placenta
- ❖ Fetal/maternal ratio: 0.9



10/19/2011

Adapted by Dr. Amitai from: Amitai, IMAJ (1999) 1: 250

29

Exposure to lead occurs prenatally, and after birth, by ingestion and inhalation of lead from different sources.

Prenatal exposure is determined by maternal body burden of lead.

Lead can be mobilized from maternal bone during pregnancy and readily crosses the placenta. This slide summarizes data on 70 mother–newborn pairs in Israel, where lead level was measured both in a blood sample from the mother at delivery, and from the cord blood, representing the exposure of the newborn during pregnancy.

There was a strong correlation ( $r^2 = 0.68$ ) between the blood lead level in the mothers and their newborns. On average, the newborns' blood lead levels were about 90% of that of their mothers (fetal/maternal ratio of 0.9).

<<NOTE TO USER: For more information see module on lead.>>

<<NOTE TO USER: For more information on prenatal exposures to other heavy metals, see modules on mercury and other heavy metals.>>

Ref:

•Amitai Y. Prenatal lead exposure in Israel: an international comparison. *Israel Medical Association Journal*, 1999 1:250.

Slide kindly provided by Dr. Amitai

## Developmental & environmental origins of adult disease

### EXAMPLE: LEAD

#### Risk for spontaneous abortion by maternal blood lead levels

- Evaluation of risk of spontaneous abortion from low or moderate lead exposures
- Nested case control study in Mexico (1994-1996) with 668 pregnant women
- Odds ratio for spontaneous abortion was 1.8 (95% confidence interval = 1.1, 3.1) for every 5 microg/dL increase in blood lead.

*Borja-Aburto VH, et al. Am J Epidemiol 1999;150:590-597.*

10/19/2011

30

This study in Mexico showed the risks of fetal death in relation to lead in blood. Lead bonds to calcium and is deposited in the bones. During pregnancy, calcium is released from the bones and so is lead, which is then free to circulate in the body. Lead has also been associated with decreased IQ and neurodevelopmental delays.

<<READ SLIDE>>

<<NOTE TO USER: For more information see modules on lead and neurodevelopment.>>

Ref:

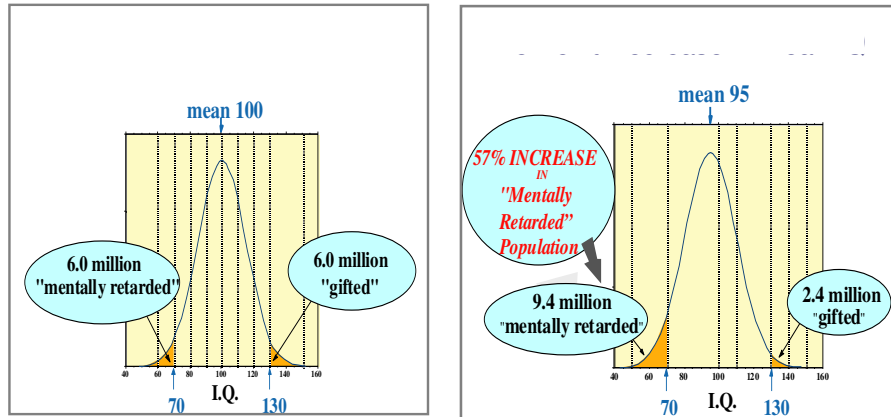
• Borja-Aburto VH, et al. Blood lead levels measured prospectively and risk of spontaneous abortion. *Am J Epidemiol*, 1999;150:590-597.

*Studies of low to moderate level lead exposures have reported mixed findings regarding the risk of spontaneous abortion, despite lead's abortifacient properties at very high doses. To evaluate the risk of spontaneous abortion from low or moderate lead exposures, a nested case-control study was conducted within a cohort of pregnant women in Mexico City, 1994-1996. During their first trimester, 668 women enrolled, were interviewed, and contributed blood specimens. Pregnancies were followed by home visits or telephone calls. Spontaneous abortions before week 21 (n = 35) were matched with pregnancies that survived beyond week 20 (n = 60) on maternal age, hospital, date of enrolment, and gestational age at enrolment. Mean blood lead levels were 12.03 microg/dL for cases and 10.09 microg/dL for controls (p = 0.02). Odds ratios for spontaneous abortion comparing 5-9, 10-14, and > or =15 microg/dL with the referent category of <5 microg/dL of blood lead were 2.3, 5.4, and 12.2, respectively, demonstrating a significant trend (p = 0.03). After multivariate adjustment, the odds ratio for spontaneous abortion was 1.8 (95% confidence interval = 1.1, 3.1) for every 5 microg/dL increase in blood lead. Low to moderate lead exposures may increase the risk for spontaneous abortion at exposures comparable to US general population levels during the 1970s and to many populations worldwide today; these are far lower than exposures encountered in some occupations.*

• WHO. Childhood lead poisoning. WHO, 2010. Available at [www.who.int/ceh/publications/childhoodpoisoning/en/index.html](http://www.who.int/ceh/publications/childhoodpoisoning/en/index.html) - accessed March 2011.

## Developmental & environmental origins of adult disease

### EXAMPLE: LEAD - SIGNIFICANCE OF 5 POINT IQ REDUCTION



[www.preventingharm.org/execsum.html](http://www.preventingharm.org/execsum.html)  
Schettler, Greater Boston Physicians for Social Responsibility, 2000

10/19/2011

31

A 5-point loss in IQ might not affect the ability of an individual to live a productive life. But if that loss is experienced by an entire population, the implications for that society could be profound. Professor Bernard Weiss, a behavioural toxicologist at the University of Rochester, New York, USA, examined the societal impact of seemingly small losses of intelligence. Imagine an unaffected population numbering 260 million people (such as that of the USA) with an average IQ of 100 and a standard deviation of 15 (left-hand graph). In that population there would be 6 million people with IQs above 130 and 6 million below 70.

A decrease in average IQ of 5 points would shift the distribution to the left (right-hand graph). The number of people scoring above 130 would decline by 3.6 million while the number below 70 would increase by 3.4 million.

IQ: intelligence quotient

*Picture adapted from Schettler T. In Harm's Way. Greater Boston Physicians for Social Responsibility, 2000.*

*Used with permission.*

<<NOTE TO USER: For more information see modules on lead and neurodevelopment.>>

## Developmental & environmental origins of adult disease

### **METHYLMERCURY: POWERFUL NEURODEVELOPMENTAL TOXICANT**

- ❖ **Impedes nerve cell division and migration**
- ❖ **Binds with microtubules required for neuronal development**
- ❖ **Binds to and distorts DNA & RNA**



EHP

10/19/2011

32

Toxicodynamics refers to the type of injury done to tissues.

The fetal brain is the most sensitive human tissue to damage from this powerful neurodevelopmental toxicant. In order for the brain to develop properly, an orderly process of cell differentiation and migration must occur to produce a specific and highly ordered brain architecture. Methylmercury interferes with this process by binding to critical structures such as microtubules that are crucial to normal cell division and migration. It also binds to and distorts important molecules like DNA and RNA.

*Ref:*

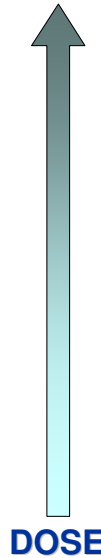
•Casarett and Doull, *Toxicology – The basic science of poisons*. 5<sup>th</sup> Ed..Ed: Klaassen., McGraw-Hill, 1996.

*Picture: Environmental Health Perspectives (2002) 110 (6)*

## Developmental & environmental origins of adult disease

### EFFECTS OF PRENATAL METHYLMERCURY EXPOSURE

- ❖ Mental retardation
- ❖ Ataxia & cerebral palsy
- ❖ Seizures
- ❖ Vision & hearing loss
- ❖ Delayed developmental milestones
- ❖ Language disorders
- ❖ Deficits in fine motor function
- ❖ Visual spatial disabilities
- ❖ Memory problems
- ❖ Low cardiac rate variability
- ❖ ? Blood pressure



10/19/2011

33

Depending on the dose and timing of exposure during gestation, the effects may be severe and immediately obvious, or subtle and delayed.

Neurological symptoms include mental retardation, ataxia and cerebral palsy, seizures, vision and hearing loss, delayed developmental milestones, language disorders, and problems with motor function, visual spatial abilities, and memory.

Results from long-term cohort studies suggest that the cardiovascular system is also at risk—with decreased heart rate variability as methylmercury exposure increases. One study suggested diastolic blood pressure in boys may be associated with prenatal methylmercury exposure, but the association needs more study.

The full expression of these health effects of methylmercury can be delayed and deficits are often irreversible.

Ref:

•Casarett and Doull, *Toxicology – The basic science of poisons*. 5<sup>th</sup> Ed..Ed: Klaassen., Mc-Graw-Hill, 1996.

•Grandjean P et al. Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. *J Pediatr*. (2004) 144(2):169.

To determine whether heart function in childhood is affected by exposure to methylmercury (MeHg) from seafood. Prospective study of a Faroese birth cohort (N=1022). Examinations at ages 7 and 14 years included blood pressure, heart rate variability (HRV) and its frequency components of autonomic origin, and brainstem auditory evoked potentials (BAEPs). Mercury concentrations were determined in cord blood and in the child's hair. Results: Both low-frequency (LF) and high-frequency (HF) activities decreased by about 25% from 7 to 14 years; they correlated well with the blood pressures. A doubling of prenatal MeHg exposure was associated with a decrease in LF and HF powers of about 6.7% (P=.04) and in the coefficient of variation of the electrocardiographic R-R interval of 2.7% (P=.04) at age 14 years. No discernible effect on blood pressure was apparent. Decreased LF variability was associated with increased latency of BAEP peak III, but adjustment for MeHg exposure substantially attenuated this correlation. Conclusions: Methylmercury exposure was associated with decreased sympathetic (LF) and parasympathetic (HF) modulation of the HRV. Parallel MeHg-related delays of BAEP latencies may be caused by underlying MeHg neurotoxicity to brainstem nuclei.

•Thurston SW et al. Does prenatal methylmercury exposure from fish consumption affect blood pressure in childhood? *Neurotoxicology*. 2007 Sep;28(5):924-30.

**INTRODUCTION:** Prenatal exposure to organic methylmercury (MeHg) from seafood consumption has been reported to increase children's blood pressure (BP). A report from the Faroe Islands noted significantly increased diastolic and systolic BP in 7-year-old children as prenatal MeHg exposure increased. The Faroese diet includes sea mammals that contain MeHg, cadmium, and other pollutants. We examined this relationship in the Seychelles Islands to determine if it was present in a society exposed primarily to MeHg from consuming ocean fish. **METHODS:** We obtained BP at ages 12 and 15 years on children with known prenatal MeHg exposure enrolled in the Seychelles Child Development Study (SCDS). We examined the association between prenatal MeHg exposure and BP using longitudinal models and linear regression adjusted for relevant covariates. **RESULTS:** Blood pressure at both ages was associated with BMI, height and maternal hypertension during pregnancy as expected. No association between prenatal MeHg exposure and BP was present in girls at either age or in either sex at age 12 years. At age 15 years diastolic BP in boys increased with increasing prenatal MeHg exposure, while systolic BP was unaffected. **SUMMARY:** It is unclear whether the association between prenatal MeHg exposure and diastolic BP seen in 15-year-old boys is of biological significance or if it is a chance finding. However, the finding is intriguing and deserves further study.

## Developmental & environmental origins of adult disease

### **MINAMATA DISEASE: METHYLMERCURY EXPOSURE IN PREGNANCY**

- ❖ Mothers often asymptomatic
- ❖ Microcephaly
- ❖ Cerebral palsy/spasticity
- ❖ Mental deficits
- ❖ Malformation of ears, heart, skeleton, eyes



**Minamata Bay, Japan**

*Courtesy of Dr. Stephan Boese-O'Reilly 2001*

10/19/2011

34

Knowledge about the extreme vulnerability of the fetus to methylmercury began with the Minamata Bay, Japan experience. The bay was heavily contaminated with methylmercury from industrial discharge. Fish bioconcentrated the toxicant and mothers acquired high blood levels from eating fish from the bay. While the mothers were usually without symptoms of mercury poisoning, their babies were born severely damaged with microcephaly, cerebral palsy, severe mental retardation, seizure disorders, blindness, deafness and other malformations.

It is interesting to know that for many years, cats eating the fish in Minamata Bay area suffered a "strange" neurological disease.

Information on the Japanese Institute on Minamata Disease can be found at [www.nimd.go.jp/english/index.htm](http://www.nimd.go.jp/english/index.htm)

*Picture: Courtesy of Stephan Boese-O'Reilly. Minamata Bay Japan, 2001.*

*Ref:*

•Yorifuji T et al. Long-term exposure to methylmercury and neurologic signs in Minamata and neighboring communities. *Epidemiology*. 2008 Jan;19(1):3-9.

*BACKGROUND: It is well known that large-scale poisonings caused by methylmercury occurred in Japan (Minamata, in the 1950s) and Iraq. However, in contrast to Iraq, there have been few sound epidemiologic studies in Minamata. We evaluated the effect of methylmercury on neurologic signs using data from a 1971 population-based study. METHODS: Villages in 3 areas were selected for study: the Minamata area (a high-exposure area), the Goshonoura area (a medium-exposure area), and the Ariake area (a low-exposure area). We used place of residence as the exposure indicator. We examined associations between methylmercury exposure and the following neurologic signs measured on clinical examination: paresthesia of whole body, paresthesia of extremities, paresthesia around the mouth, ataxia, dysarthria, tremors, and pathologic reflexes. RESULTS: Total population was 1120 in the high-exposure villages, 1845 in the medium-exposure villages, and 1165 in the low-exposure villages. In the Minamata area, 87% (n=833) of the eligible population (age 10 years and older) participated in the 1971 investigations, in the Goshonoura area, 93% (n = 1450), and in the Ariake area, 77% (n = 755). Compared with subjects in the Ariake area, the subjects in the Minamata area manifested neurologic signs more frequently. The highest prevalence odds ratio was observed for paresthesia around the mouth (110; 95% confidence interval = 16-820). Although residents in the Goshonoura area had been exposed less heavily than those in the Minamata area, Goshonoura residents also had increased prevalence of neurologic signs. CONCLUSION: Long-term exposure to methylmercury has a strong adverse impact on neurologic signs among residents in a local community.*

## Developmental & environmental origins of adult disease

### OTHER EXAMPLES

- ❖ **Radiation:** exposure *in utero* in Nagasaki led to mental retardation and small head size
  
- ❖ **Ethyl alcohol:** array of congenital malformations in children of alcoholic mothers – Fetal alcohol spectrum disorder
  - Mental retardation
  - Microcephaly
  - Short palpebral fissures
  - Intrauterine and postnatal growth retardation.
  
- ❖ **Noise, heat:** impacts that harm mother's health can indirectly have detrimental effects on fetus.

10/19/2011

35

<<READ SLIDE>>

<<NOTE TO USER: For more information see modules on noise, radiation, occupational health>>

*Refs:*

- Haelterman E et al. Population-based study on occupational risk factors for preeclampsia and gestational hypertension. *Scand J Work Environ Health*. 2007, 33(4):304-17.
- Miller RW. How environmental hazards in childhood have been discovered: carcinogens, teratogens, neurotoxicants and others, *Pediatrics*, 2004, 113 (4): 945.

*Review of the literature reveals that environmental hazards cause adverse health effects that include sterility, infertility, embryotoxicity, low birth weight, skin lesions, neurodevelopmental defects, immunologic disorders, cancer, and fear of late effects. They have been identified mostly by astute practitioners but also by a bacteriologist, an animal experimentalist, 5 factory workers in childless marriages, and a tipsy bystander in an economically impoverished area of Baltimore. Dust on a parent's work clothes has transported a hazard at work to a hazard at home (lead, asbestos, and chlordecone). Causality is established by showing a dose-response effect and reproducing the effect in studies of other exposed groups or by using another epidemiologic method, eg, prospective instead of retrospective study. Also, the findings should be biologically plausible and not attributable to a concomitant variable such as cigarette smoking. Contrary to front-page newspaper headlines, incidence rates for childhood leukemia are not rising. Preserving specimens for future studies has been valuable: blood from people who were exposed to dioxin in Seveso, Italy; mummified umbilical cords containing methyl mercury at Minamata Bay, Japan; and Guthrie dried blood spots to screen retrospectively for 43 genetic disorders and a specific prenatal cytogenetic abnormality in some children with 1 form of leukemia. Recommendations are given for enhancing interest in environmental hazards and their discovery by clinicians.*

## Developmental & environmental origins of adult disease

### **ENDOCRINE DISRUPTING CHEMICALS**

Exogenous substance or mixture that alters the function(s) of the hormonal system and consequently causes adverse effects in an intact *organism*, or its *progeny* or its *sub-population*

#### Natural

- **Phytoestrogens**
- **Fungal estrogens**

#### Synthetic

- **Hormones**
- **Some pesticides**
- **Industrial by-products ("dioxin-like")**
- **Pharmaceuticals**
- **Some persistent organic pollutants (POPs)**

10/19/2011

36

Some substances are suspected to alter the function of the hormonal system. The substance can be natural or synthetic.

**<<NOTE TO USER: For more information see module on endocrine disruptors.>>**

*Refs:*

•Diamanti-Kandarakis E et al. Endocrine disrupting chemicals. An Endocrine Society Scientific Statement. *The Endocrine Society*. 2009.

•WHO. Global Assessment of the State-of-the-Science of Endocrine Disruptors. *WHO*, Geneva, Switzerland, 2002.

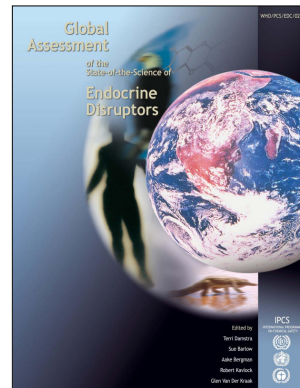
## Developmental & environmental origins of adult disease

### EXAMPLES OF EFFECTS ON WILDLIFE

REPTILES: decline in alligator population by 90% after dicofol, dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE) chemical spill

- ❖ Smaller penis size
- ❖ Abnormal gonad morphology
- ❖ Altered sex steroid concentrations

FISH: reproductive alterations when exposed to sewage treatment waste



10/19/2011

WHO

37

We have many examples about endocrine disruptors from wildlife. WHO did an assessment of the state of the science on endocrine disruptors and analyzed the case of endocrine disruptors we are aware of (mostly because of incidents/accidents in history) and the many suspicions we have about others and their effect on human health.

#### *Refs:*

- Guillette Jr, L J et al. Gonadal steroidogenesis in vitro from juvenile alligators obtained from contaminated or control lakes. *Environmental Health Perspectives*, 1995, 103(4), 31-36.
- WHO. Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO, Geneva, Switzerland, 2002.

## Developmental & environmental origins of adult disease

### EFFECTS OF ENDOCRINE DISRUPTING CHEMICALS ON HUMAN HEALTH

- ❖ Immune system
- ❖ Neurological system
- ❖ Reproductive
- ❖ Developmental

10/19/2011

38

The toxic effects of endocrine disruptors (EDCs) may include effects on the developmental, immune, neurological, and reproductive systems. The research and evidence supporting these effects do not point to a cause and effect type relationship due to a lack of exposure data. Instead, many of them are inferred from animal studies and observations made in human studies.

Diethylstilbestrol (DES) is one of the most well known endocrine disruptors. It was prescribed to women in the early 1900s to prevent miscarriages. It is a synthetic estrogen that was taken in high doses. Studies later showed that when pregnant women took this compound during a specific developmental period and exposed the fetus in utero, many anatomic reproductive tract abnormalities were observed in future generations as well as increased incidence of some cancers. This case study led to the idea that synthetic compounds can affect endocrine systems profoundly.

A number of observations have been made about EDCs effects on the immune system, neurological system, reproductive and developmental systems.

Immune system effects have been observed in children after in utero exposure to polychlorinated biphenyls (PCBs). A higher prevalence of respiratory symptoms and other infectious diseases were seen. These effects have been seen only after high dose exposures. It is thought that the mechanism involves thymic atrophy and therefore decreased thymocytes in neonates and infants.

In terms of neurologic effects, we do know that many chemicals at high exposures can cause short term neurologic effects potentially mediated by endocrine mechanisms. For low dose effects, it is known that PCB interferes with the thyroid receptor in animal studies but human studies have not been able to show consistent exposure effect data.

Reproductive abnormalities have been seen with chemicals such as DES that we just mentioned but many more are hypothesized to occur. These include declining sperm counts and increasing incidence of male reproductive tract abnormalities and testicular cancer.

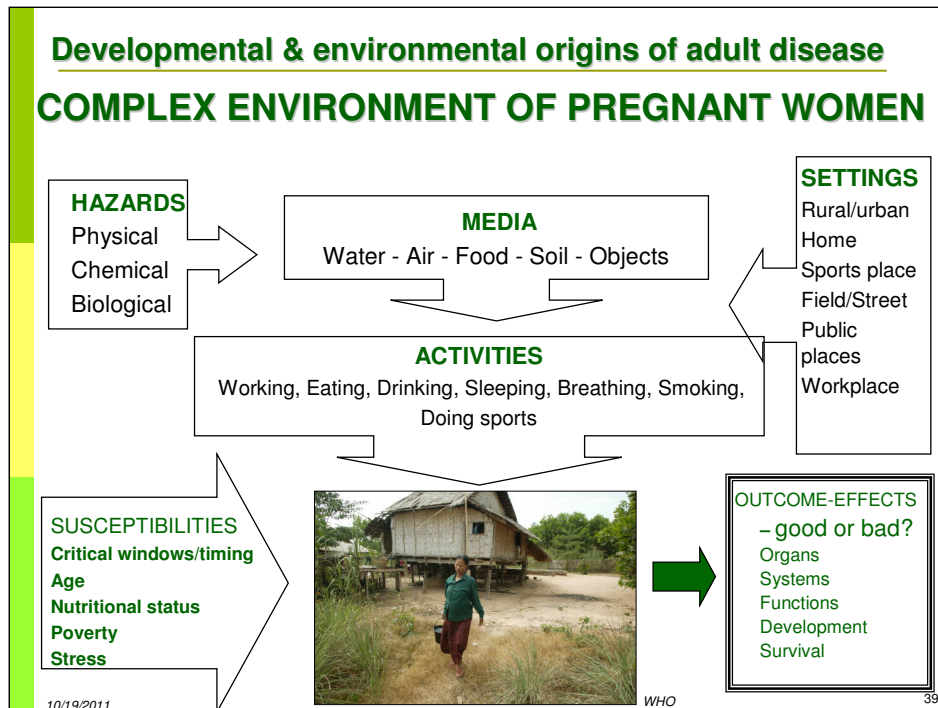
For the reproductive system, it has been postulated that a number of male reproductive system effects including decreasing sperm production, increasing rates of hypospadias and cryptorchidism can be attributed to EDCs.

We do know that high dose exposures to some chemicals such as chlordecone and dibromochloropopane have caused infertility in adult men but do not know the mechanism of action.

Developmental abnormalities encompasses many different systems but usually growth and psychologic testing are used as indicators of developmental status. The evidence supporting neurodevelopmental abnormalities with PCB exposure is judged to be moderate in nature.

*Ref:*

•WHO. Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO, Geneva, Switzerland, 2002.



In this summary slide, we see the complexity of the issues related to the pregnant woman's environmental health. Hazards (physical, chemical, biological – in many cases favoured by social factors) are introduced into environmental media (water, air, food, soil and objects) with variable efficiency in different settings (urban and rural: home, school, field, playground, street and workplace). The future mother's activities brings her into contact with these hazards. And, as discussed, the mother's environment determines the fetal environment and has an impact on fetal development and future disease.

<<READ SLIDE.>>

Depending upon the individual susceptibility of the mother based upon age, general health and social supports, the exposure may cause harm ranging from subtle changes in function to death.

Image: WHO

## **Developmental & environmental origins of adult disease IF PREGNANT**

Many pregnancy/birth problems could be avoided through:

- **Family planning,**
- **Balanced, organic diet**
- **Management of maternal health problems**
- **Avoiding maternal infection**

Usual advice:

- ✓ Folic acid in flour to prevent neural tube defects,
- ✓ Iodine in salt to prevent congenital hypothyroidism,
- ✓ Vit B<sub>12</sub> (methyl donor important for DNA and protein modification) around conception
- ✓ Rubella vaccination to prevent congenital rubella syndrome.

Doctors traditionally give advice to pregnant women that includes, among others, taking folic acid, vitamins and getting rubella vaccinations (if not yet vaccinated).

### *Refs:*

- Fleming TP et al. The embryo and its future. *Biology of Reproduction*, 2004, 71: 1046.
- The March of Dimes global report on birth defects, the hidden toll of dying and disabled children.  
Available at [www.marchofdimes.com/professionals/871\\_18587.asp](http://www.marchofdimes.com/professionals/871_18587.asp) – accessed May 2011.

## Developmental & environmental origins of adult disease

### **HOW TO REDUCE EXPOSURE? Examples of advice for patients**

- ❖ Don't smoke! Nor stay near smokers
- ❖ No alcohol during pregnancy
- ❖ No use of drugs
- ❖ Consult your doctor before taking medications
- ❖ Eat food without additives
  - ...organic (without pesticides and preservatives)
  - if not possible, wash your fruits and vegetables
- ❖ Avoid fish rich in persistent organic pollutants and mercury (bigger fish)
- ❖ Observe fish advisories on mercury
- ❖ Don't use solvents – avoid paints
- ❖ Reduce the number of chemical cleaners at home
- ❖ Avoid heating plastic food containers



WHO

10/19/2011

41

Other advice that could consider environmental risk factors could include

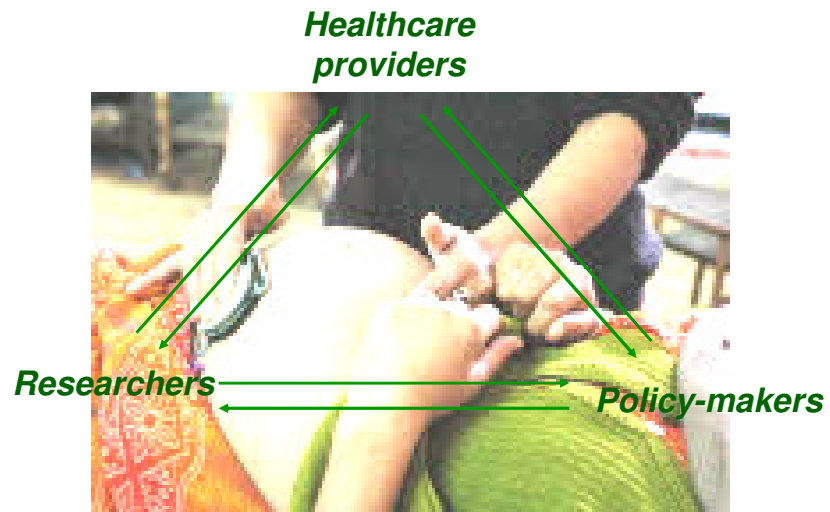
<<READ SLIDE>>

<< NOTE TO USER: Please adapt the advice to your own context/region.>>

Ref:

•EWG. Body burden: The pollution in newborns. *EWG*, 2005

## Developmental & environmental origins of adult disease



As we await for the results of long-term studies on fetal and newborn health that will provide more specific answers, health care providers, researchers and policy-makers are in a unique role to work with one another and making change happen.

## **Developmental & environmental origins of adult disease**

### **Providing safer and healthier environments for women**

#### **Solutions are multiple – *more or less feasible*- Tools are available**

- ❖ Reach the decision-making and donors with new information: women's health & environment – *what is the evidence? Which tools are available? How to take action?*
- ❖ Reach the pre/post-graduates with new knowledge – and promote research – NEW INFORMATION!
- ❖ Reach the communities – women's groups: "*don't hide, don't scare*"
- ❖ Set up strategic partnerships for action: research, scientific bodies, NGOs...
- ❖ *Promote and adopt an environmentally-minded "personal" agenda...*

#### **<<READ SLIDE>>**

##### Refs:

- WHO. Children's health and the environment: a global perspective. Pronczuk J, ed. *WHO*, Geneva, 2005
- WHO/UNEP. Healthy environments for healthy children. Key messages for action. *WHO*, Geneva, 2010. Available at [www.who.int/ceh/publications/hehc\\_booklet/en/index.html](http://www.who.int/ceh/publications/hehc_booklet/en/index.html) – accessed May 2011.

## **Developmental & environmental origins of adult disease**

### **ACKNOWLEDGEMENTS**

WHO is grateful to the US EPA Office of Children's Health Protection for financial support that made this project possible and for some of the data, graphics and text used in preparing these materials for a broad audience. Further support was kindly provided by the UK Department of Health.

#### **First draft prepared by Marie-Noel Bruné, MSc. (WHO)**

**With the advice of the Working Group Members on the Training Package for the Health Sector: Cristina Alonzo MD (Uruguay); Yona Amitai MD MPH (Israel); Stephan Boese-O'Reilly MD MPH (Germany); Stephania Borgo MD (ISDE, Italy); Irena Buka MD (Canada); Ernesto Burgio (ISDE, Italy); Lilian Corra MD (Argentina); Ligia Fruchtengarten MD (Brazil); Amalia Laborde MD (Uruguay); Jenny Pronczuk MD (WHO) Christian Schweizer TO (WHO/EURO); Kathy Shea MD (USA).**

**Reviewers: Prof. Dr. Michael Hanson (UK), Prof. Dr. Sir Peter Gluckman (New Zealand), Prof. Dr. Oriol Vall Combelles (Spain) Dr Huw Brunt (UK), Prof Gary Coleman (UK), Dr Raquel Duarte-Davidson (UK), Dr Elaine Lynch Farmery (UK), Alison M Good BSc Dip Med Tox MSc (UK), Dr Mark Griffiths (UK), Dr John Thompson (UK), Dr Laura Yates (UK)**

**WHO Project coordination: Ruth A. Etzel, MD PhD  
Marie-Noël Bruné, MSc**

**10/19/2011 Latest update: October 2011**

## **Developmental & environmental origins of adult disease**

### ***DISCLAIMER***

- ❑ The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
- ❑ The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.
- ❑ The opinions and conclusions expressed do not necessarily represent the official position of the World Health Organization.
- ❑ This publication is being distributed without warranty of any kind, either express or implied. In no event shall the World Health Organization be liable for damages, including any general, special, incidental, or consequential damages, arising out of the use of this publication
- ❑ The contents of this training module are based upon references available in the published literature as of its last update. Users are encouraged to search standard medical databases for updates in the science for issues of particular interest or sensitivity in their regions and areas of specific concern.
- ❑ If users of this training module should find it necessary to make any modifications (abridgement, addition or deletion) to the presentation, the adaptor shall be responsible for all modifications made. The World Health Organization disclaims all responsibility for adaptations made by others. All modifications shall be clearly distinguished from the original WHO material.